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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,422	09/18/2006	Kamal Azzaoui	NOV-15-US	4841

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EXAMINER	
HAVLIN, ROBERT H	
ART UNIT	PAPER NUMBER
1626	
MAIL DATE	DELIVERY MODE
08/25/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,422	AZZAOUI ET AL.	
	Examiner	Art Unit	
	ROBERT HAVLIN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-10* is/are pending in the application.

4a) Of the above claim(s) *4,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims: Claims 1-6, and 8-10 are currently pending.

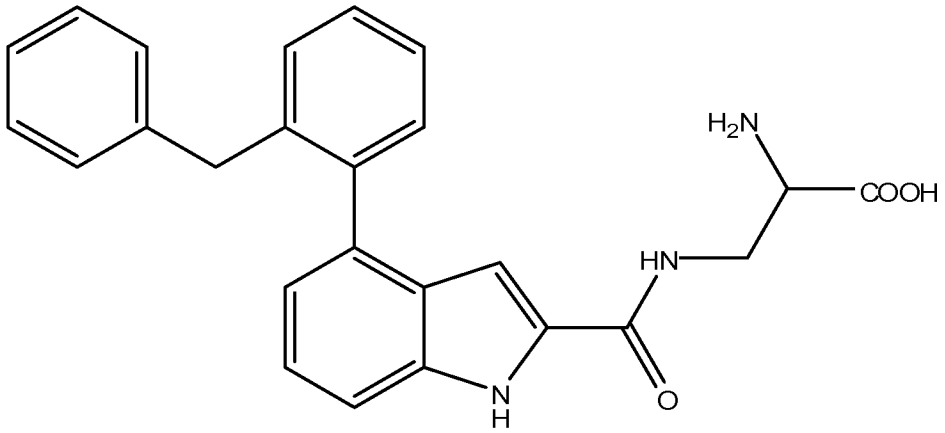
Priority: This application is a 371 of PCT/EP05/00541 (01/20/2005) and claims foreign priority to UNITED KINGDOM 0401332.2 (01/21/2004).

IDS: The IDS dated 7/19/06 was considered.

Election/Restrictions

1. Applicant's election of Group I (claims 1-6, and 8) in the reply filed on 6/10/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant also elected the compound of Example 2 (the compound of formula I from page 1, lines 19-22 wherein R1 is 2-benzyl-phenyl and R2 is hydrogen) corresponding to the following structure determined to read on claims 1-3, 5-6, and 8:



2-amino-3-(4-(2-benzylphenyl)-1*H*-indole-2-carboxamido)propanoic acid .

As detailed in the following rejections, the generic claim encompassing the elected species was not found patentable. Therefore, the provisional election of

species is given effect, the examination is restricted to the elected species only, and claims not reading on the elected species are held withdrawn. Accordingly, claims 4, 9, and 10 are hereby withdrawn.

Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection through amendment, the amended Markush-type claim will be reexamined to the extent necessary to determine patentability of the Markush-type claim. See MPEP 803.02.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 5-6, and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds identified as having relevant experimental data, such as EC50 data, does not reasonably provide enablement for the asserted utility of the entirety of the claim scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of affecting enzymes.

> "[An inventor] must not be permitted to achieve . . . dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph

> of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, the critical element here how broad the claims are compared to the level of unpredictability in the art.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of Invention. The nature of the invention involves pharmaceutical compounds for affecting/modulating enzymes.

Scope of the Invention. The scope of the invention is a possibly huge genus of compounds which is an agonist of the S1P4 receptor with specific selectivity.

State of the Art and Level of Skill in the Art. Although the level of skill in the art is very high, affecting enzymes is a very unpredictable art. Kubinyi (3D QSAR in Drug Design: Ligand-Protein Interactions and Molecular Similarity, Vol 2-3, Springer, 1998, 800 pages) teaches that very slight perturbations in the structure of an inhibitor (such as the addition of a methyl group or inversion of a chiral center, see p. 243) can have radical effects on the binding to an enzyme.

Number of Working Examples and Guidance Provided by Applicant. The applicant provides data for a single compound of Example 2 as reproduced below:

The EC_{50} values (in μM) for the compound of example 2 in CHO cells or in CHO cells expressing various S1P receptors is shown in Table 2 below:

TABLE 2

	CHO	S1P1	S1P2	S1P3	S1P4	S1P5
Calcium mobilization assay	>6	>6	>6	>6	0.01	2.4
GTPγS binding assay	>10	>10	>10	>10	0.25	>10

The compounds of the invention are, therefore, useful in the treatment and/or prevention of diseases or disorders mediated by lymphocytes interactions, e.g. in transplantation, such as acute or chronic rejection of cell, tissue or organ allo- or xenografts or delayed graft function, graft versus host disease, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I

...

Unpredictability of the Art and Amount of Experimentation. The art of using pharmaceuticals to affect enzymes is highly unpredictable as described by Kubinyi. In nearly every case, the skilled artisan could not predict *a priori* whether a given pharmaceutical would inhibit/modulate an enzyme. When small variations in structure such as the addition of a methyl group has radical effects on the binding of an inhibitor/modulator, without specific guidance or correlations indicating how the structure of species affects its ability to bind to an enzyme the scope of enablement is constrained to compounds showing substantial similarity to those actually demonstrated to be useful. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the large number of compounds within the claimed scope.

Considering the above factors, the claims are clearly not enabled for the full scope of the compounds claimed. The examiner recommends either amending the claim scope to only those compounds closely resembling the compounds actually tested and disclosed in the specification or provide additional data and/or structural correlations to guide one of ordinary skill in the art to compounds possessing the asserted utility.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 5, and 6 rejected under 35 U.S.C. 102(b) as being anticipated by Rios Candelore et al. (Biochemical and Biophysical Research Communications (2002), 297(3), 600-606).

The Rios Candelore et al. teaches PhS1P as pharmaceutical agonist to S1P4 (page 605) and acts with 10-fold selectivity difference from S1P1 as measured by EC50 (page 602). Thus the claims are anticipated.

Conclusion

The claims are not in condition for allowance.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/
Examiner, Art Unit 1626